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(54) **Novel benzoic acid derivatives and process for preparing the same.**

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JOURNAL OF MEDICINAL CHEMISTRY, vol. 11, no. 3, 26th April 1968, pages 451-453, Washington, DC; I. BELSKY et al.: "Amides of silicon-containing aromaticcarboxylic acids"

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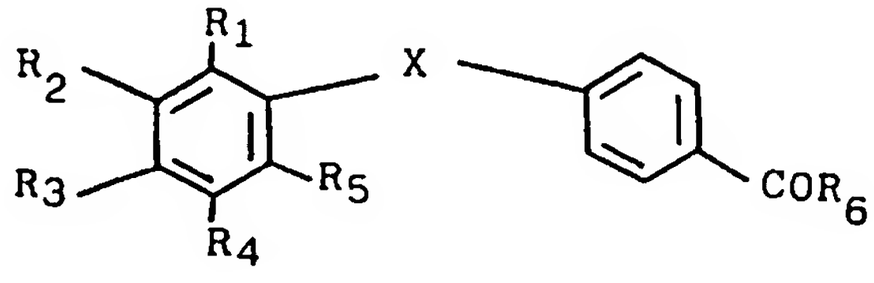
Description

1. Field of the Invention

The present invention relates to novel benzoic acid derivatives represented by the general formula (I), which have great potential as useful medicaments, and a process for preparing the same.

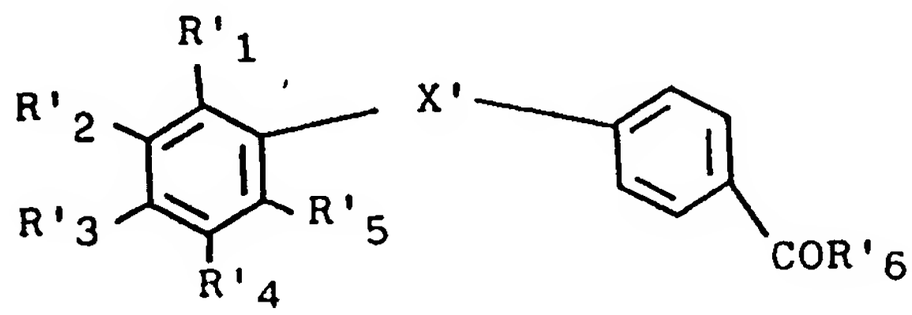


(I)

The variables in the formula are described in detail in the following.

2. Description of the Prior Art

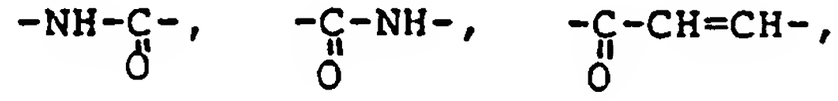
In Japan Kokai 61-22046, 61-22047 and 61-76440, it was already shown that benzoic acid derivatives represented by the general formula (II):



(II)

wherein R'_1, R'_2, R'_3, R'_4, and R'_5 are the same or different, and each represents hydrogen or middle or lower-alkyl, with the proviso that all can not be hydrogen simultaneously, and wherein two neighboring substituents may be combined with each other to form a cycloalkyl ring having 5 to 6 carbon atoms, R'_6 represents hydroxyl, lower-alkoxyl, or lower-alkylamino of the formula $-NR'_7R'_8$, wherein R'_7 and R'_8 each represents hydrogen or lower-alkyl, and X' represents a group of the formula:

-CH = CH-,



or

-N = N-,

are capable of inducing the differentiation of malignant cells, especially leukemia cells, to morphologically and functionally mature cells which cannot proliferate further, and are accordingly pharmacologically valuable and useful for treatment of malignant proliferous or immune diseases such as cancer, rheumatism, or psoriasis, and in Japan Kokai 62-215581, there are also shown related compounds. The literature also shows the activity and measurement of the activity of those compounds by the differentiation of human acute promyelocytic leukemia cells (HL-60).

Such a compound, wherein R'_2, R'_3 and R'_4 each is a middle alkyl group, especially wherein one alkyl substituent is isopropyl or butyl, and wherein two alkyl substituents R'_2 and R'_3 are combined into a ring having 5 to 6 carbon atom, is especially effective. On the other hand such a compound, wherein both of R'_3 and R'_4 are hydrogen, does not exhibit the desired activity.

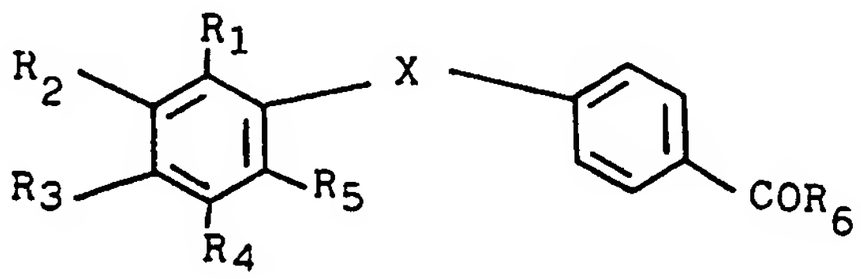
Such a compound, wherein R'_7 and R'_8 are hydrogen or methyl, and wherein R'_6 is hydroxyl or methoxy, is especially effective.

The subject of the present invention consists in : diminishing the undesirable side-effects which the above identified compounds are known to possess and providing additional new compounds having the same therapeutic potential.

US-A-3,558,683 and Belsky et al., J. Med. Chem., vol. 11, 3 (1968), p. 451-453 both describe the compound p-Trimethylsilylbenzoyl-p-carbethoxy anilide as a pharmaceutical agent.

3. Summary of the invention

It has now been found that benzoic acid derivatives represented by the formula (I):



(I)

wherein R_1 represents hydrogen or lower-alkyl, R_2 and R_4 represent hydrogen, trimethylsilyl, or trimethylgermyl, R_3 represents hydrogen, lower-alkyl, trimethylsilyl, or trimethylgermyl, R_5 represents hydrogen, lower-alkyl, acetyl, or hydroxy, at least one of R_2 and R_3 being trimethylsilyl or trimethylgermyl, and R_6 means hydroxy, lower-alkoxy, or a group of the formula $-NR_7R_8$, wherein R_7 and R_8 mean hydrogen or lower-alkyl, and X represents a group of the formula -CONH-, -NHCO-, -COO-, -OCO-, -COCH=CH-, -COCH=C(OH)-, or -CH=CH-, except the compound p-Trimethylsilylbenzoyl-p-carbethoxy anilide exhibit excellent effect as differentiation-inducing agents for neoplastic cells, especially leukemia cells.

Further, according to the present invention, there is also provided a process for preparation of the novel benzoic acid derivatives represented by the formula (I).

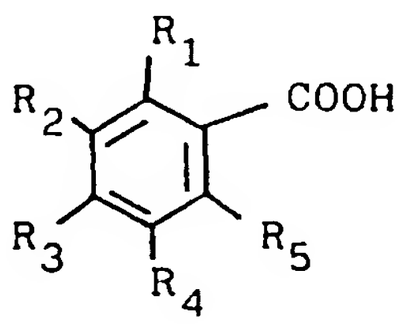
DETAILED DESCRIPTION OF THE INVENTION

By the term "lower" in formula (I) is meant a straight or branched carbon chain having 1-4 carbon atoms. Therefore, the lower-alkyl moiety of the lower-alkyl group encompassed by R_1, R_3, R_5, R_7 and R_8 is representatively methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, and tert-butyl. The lower-alkoxy moiety of the lower-alkoxy group encompassed by R_6 is representatively methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, etc.

The compounds represented by formula (I) form salts with bases. This invention includes the pharmaceutically-acceptable salts of the compounds of formula (I) and examples of these salts are salts with alkali metals such as sodium, potassium, etc., or alkaline earth metals such as calcium, etc.; salts with ammonia; and salts with organic bases such as methylamine, ethylamine, trimethylamine, triethylamine, pyridine, picoline, arginine, lysine, etc.

The novel benzoic acid derivatives represented by the formula (I) can be prepared by the following methods:

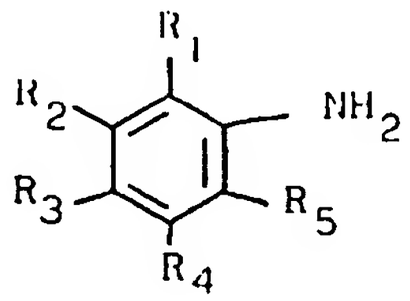
(a) a compound represented by the formula (I), wherein X represents a group of the formula -CONH-, is prepared by condensation of a functional derivatives such as the acid halide or ester, derived from a benzoic acid derivative represented by the formula (III):



(III)

wherein R_1, R_2, R_3, R_4 and R_5 have the meanings described above, with a p-aminobenzoic acid or its derivative, or

(b) a compound represented by the formula (I) wherein X represents a group of the formula -NHCO-, is prepared by condensation of an aniline derivative represented by the formula (IV):

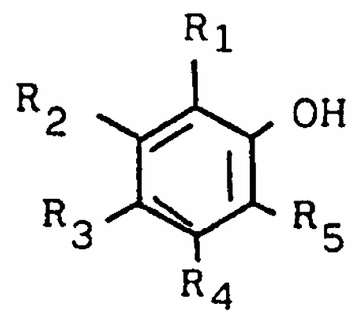


(IV)

wherein R_1, R_2, R_3, R_4 and R_5 have the meanings described above, with a functional derivative, such as the acid halide or ester, of terephthalic acid, or

(c) a compound represented by the formula (I), wherein X represents a group of the formula -COO-, is prepared by condensation of a functional derivative, such as the acid halide or ester, derived from a benzoic acid derivative represented by the formula (III), with a p-hydroxybenzoic acid or its derivative, or

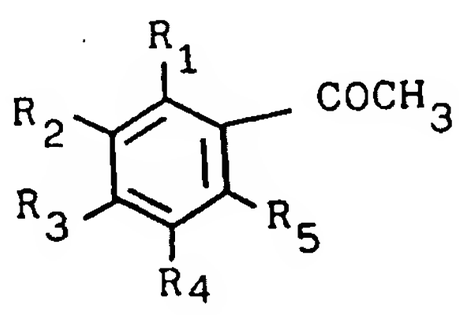
(d) a compound represented by the formula (I), wherein X represents a group of the formula -OCO-, is prepared by condensation of a phenol derivative represented by the formula (V):



(V)

wherein R_1, R_2, R_3, R_4 and R_5 have the meanings described above, with a functional derivative, such as the acid halide or ester, of terephthalic acid, or

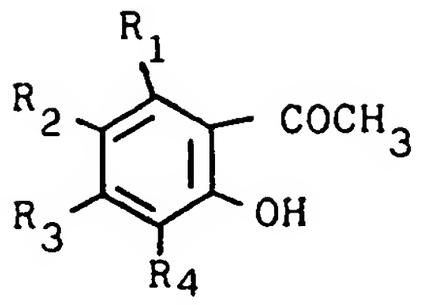
(e) a compound represented by the formula (I), wherein X represents a group of the formula -COCH = CH-, is prepared by condensation of an acetophenone derivative represented by the formula (VI):



(VI)

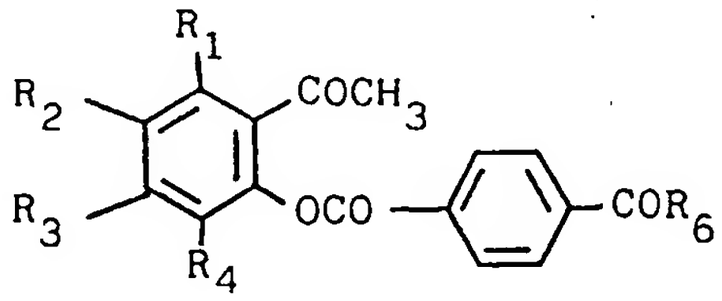
wherein R_1, R_2, R_3, R_4 and R_5 have the meanings described above, with a terephthalaldehydic acid or its derivative in the presence of a base, or

(f) a compound represented by the formula (I), wherein X represents a group of the formula -COCH = C-(OH)- and R_5 represents hydroxy, is prepared by condensation of an o-hydroxyacetophenone derivative represented by the formula (VII):



(VII)

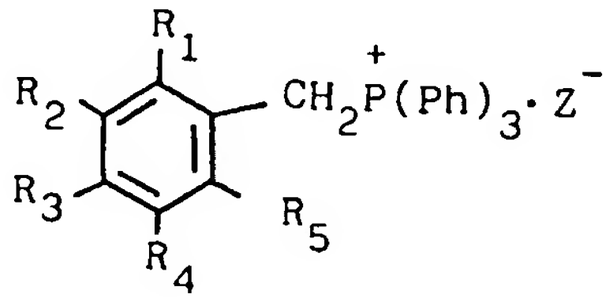
wherein R_1, R_2, R_3 and R_4 have the meanings described above, with a terephthalic acid or its derivative to give an ester represented by the formula (VIII):



(VIII)

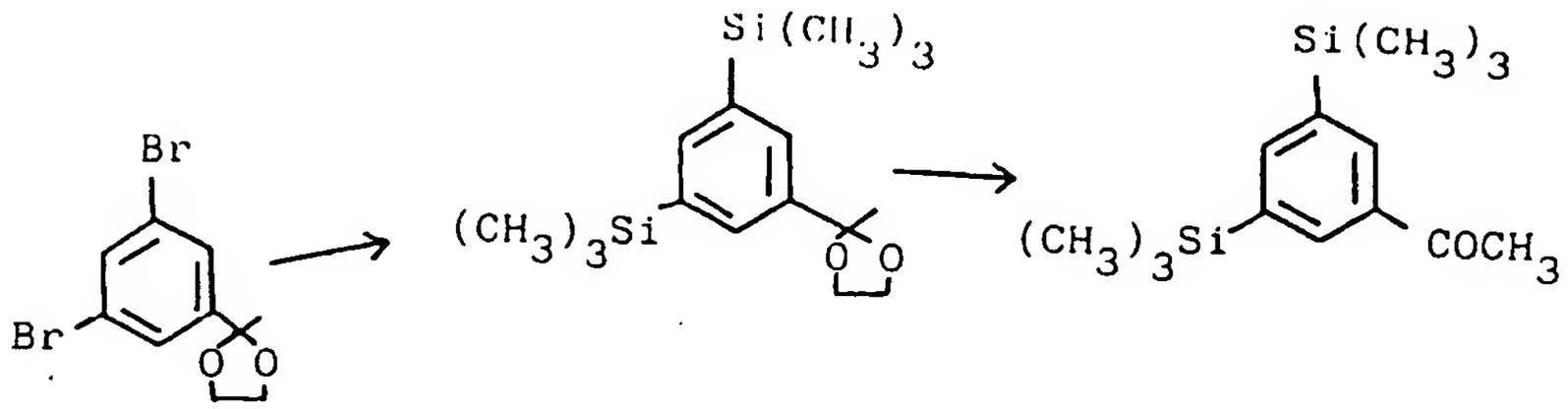
wherein R_1, R_2, R_3, R_4 and R_6 have the meanings described above, which is followed by rearrangement in the presence of an alkali catalyst, or

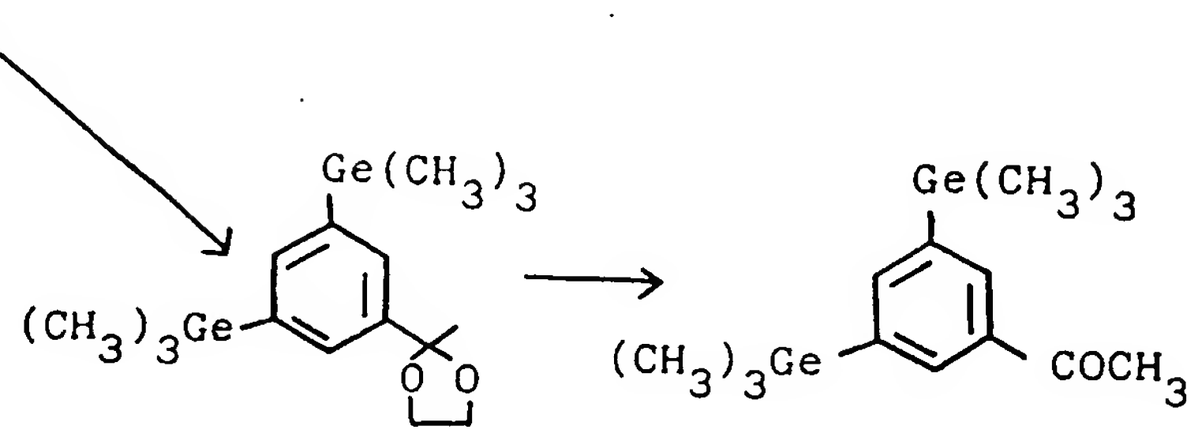
(g) a compound represented by the formula (I), wherein X represents a group of the formula -CH=CH-, is prepared by condensation of a benzylphosphonium salt represented by the formula (IX):



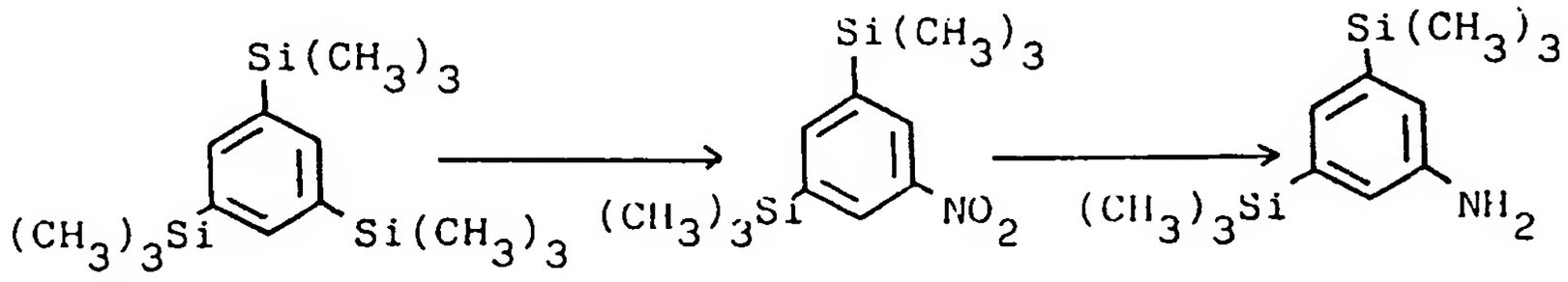
wherein R_1, R_2, R_3, R_4 and R_5 each have the meanings described above, and Z means halogen, with a terephthalaldehydic acid or its derivative in the presence of a base and, if necessary or desirable, the thus-obtained compound is hydrolyzed using an alkali catalyst.

The compounds having a trimethylsilyl or trimethylgermyl group, which are starting materials, can be prepared in the following manner. One way is using the Grignard reaction with a bromobenzene derivative and trimethylsilyl chloride or trimethylgermyl chloride, as shown in the following scheme:





Another way is using an aromatic substitution reaction, which utilizes the de-trimethylsilyl (or germyl) action of poly-trimethylsilyl (or germyl) benzene, as shown in the following scheme:



Typical examples of benzoic acid derivatives embraced by the present invention are illustrated below.
4-(3-trimethylsilylphenylcarbamoyl)benzoic acid
4-[3,5-bis(trimethylsilyl)phenylcarbamoyl]benzoic acid
4-(3-trimethylgermylphenylcarbamoyl)benzoic acid
4-[3,5-bis(trimethylgermyl)phenylcarbamoyl]benzoic acid
4-(3-trimethylsilylphenylcarboxamido)benzoic acid
4-[3,5-bis(trimethylsilyl)phenylcarboxamido]benzoic acid
4-[3,5-bis(trimethylgermyl)phenylcarboxamido]benzoic acid
methyl 4-(3-trimethylsilylphenylcarboxy)benzoate
methyl 4-[3,5-bis(trimethylsilyl)phenylcarboxy]benzoate
methyl 4-(3-trimethylgermylphenylcarboxy)benzoate
methyl 4-[3,5-bis(trimethylgermyl)phenylcarboxy]benzoate
4-[3-(3-trimethylsilylphenyl)-3-oxo-1-propenyl]benzoic acid
4-[3-[3,5-bis(trimethylsilyl)phenyl]-3-oxo-1-propenyl]benzoic acid
4-[3-(3-trimethylgermylphenyl)-3-oxo-1-propenyl]benzoic acid
4-[3-[3,5-bis(trimethylgermyl)phenyl]-3-oxo-1-propenyl]benzoic acid
4-[1-hydroxy-3-(2-hydroxy-4-trimethylsilylphenyl)-3-oxo-1-propenyl]benzoic acid
4-[1-hydroxy-3-(2-hydroxy-5-trimethylsilylphenyl)-3-oxo-1-propenyl]benzoic acid
4-[1-hydroxy-3-(2-hydroxy-4-trimethylgermylphenyl-3-oxo-1-propenyl]benzoic acid
4-[1-hydroxy-3-(2-hydroxy-5-trimethylgermylphenyl-3-oxo-1-propenyl]benzoic acid
4-[(3-trimethylsilylphenyl)ethenyl]benzoic acid
4-[[3,5-bis(trimethylsilyl)phenyl]ethenyl]benzoic acid
4-[(3-trimethylgermylphenyl)ethenyl]benzoic acid, and
4-[[3,5-bis(trimethylgermyl)pheny]ethenyl]benzoic acid

The compounds represented by formula (I) are all capable of inducing the differentiation of malignant cells, especially leukemia cells, morphologically and functionally, and can therefore be used in the treatment of tumors and cancers, leukemia, T cell malignant diseases, proliferous immune malignant dermatological diseases such as psoriasis, and immune diseas and used for the immunosuppressant in the transplantation of organs. For the therapy of cancer such as T cell lymphoma, acute promyelocytic leukemia, neuroblastoma, and carcinoma, the compounds of this invention can be used systemically, for example by injection or oral administration, in an amount of less than 5 mg/Kg/day, preferably 0.001-1 mg/Kg/day and, for therapy of dermatological diseases such as psoriasis and other dermatological diseases, topically forexample as ointments containing the compound itself or a mixture with other medicaments such as a corticosteroid, anthrarine, and UV therapeutica, in an amount of 0.1-10 mg of the active compound per gram of ointment.

The test of the activities of the compounds of this invention has been conducted by measuring the concentration required for inducing the differentiation of human acute promyelocytic leukemia cells (HL 60), according to the methods described in detail hereinafter.

Experimental

The compounds of this invention are tested according to established test procedure which shows the differentiation of malignant cells, whereby the differentiation of human acute promyelocytic leukemia cells (HL-60) and their conversion to granulocytes (myelocytes) is assayed by an observation of the morphological changes of nuclei and by the measurement of the degree of reduction of nitro-blue tetrazolium (NBT) which is induced by a test compound (Proc. Natl. Acad. Sci. USA 77, 2936 2940 (1980) with the Title: Induction of differentiation of the human promyelocytic leukemia cell line (HL-60) by retinoic acid). The HL-60 cells are cultured in plastic flasks in RPMI 1640 medium supplemented with 5% heat-inactivated fetal calf serum and antibiotics (penicillin G and streptomycin). The cells (3 $x10^4$/ml) are cultured with a compound of the present invention for 4 days. The cells are fixed and stained with Wright-Giemsa to examine the morphological changes of the nuclei.

The cells treated with the compounds of the present invention are differentiated to mature granulocytes (myelocytes, metamyelocytes and neutrophiles), just as the cells treated with retinoic acid. The biochemical activity of cells treated with the compound is measured as follows:

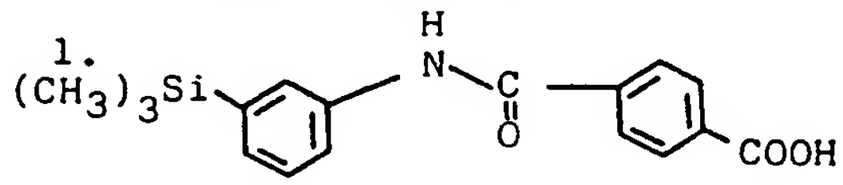
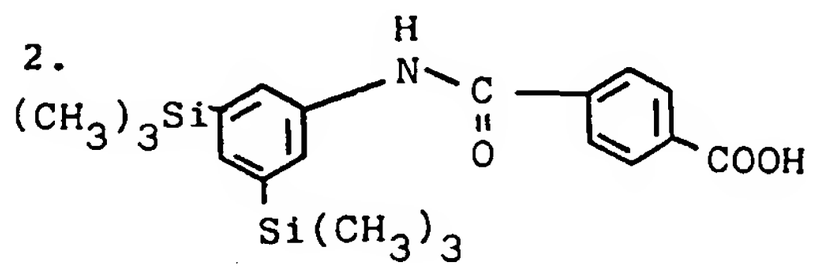
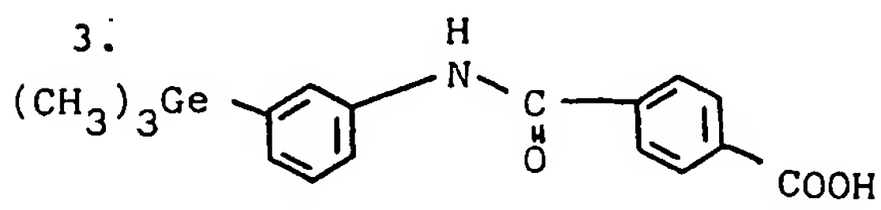
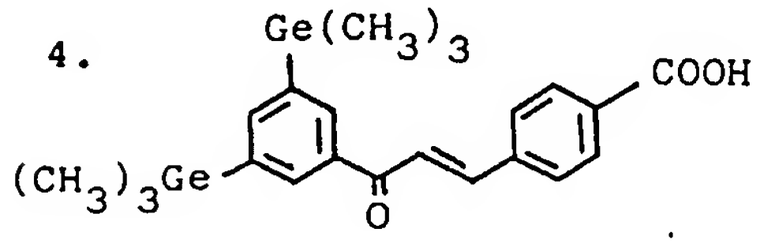
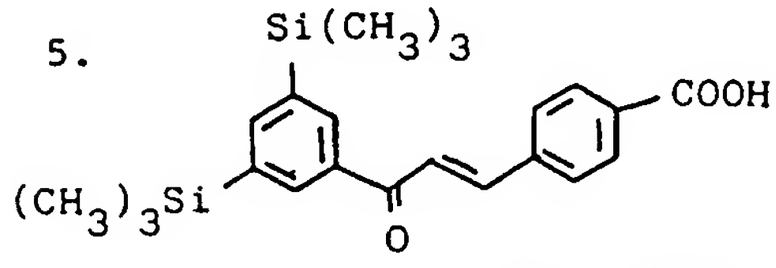
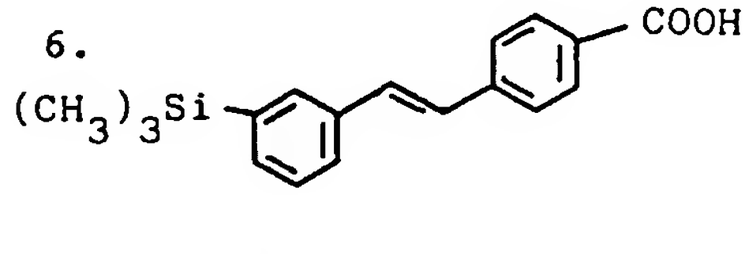
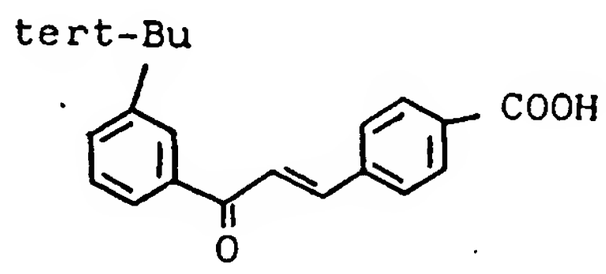
The cells after 5 days incubation are centrifuged and diluted with RPMI 1640 medium, supplemented with 5% fetal calf serum, to provide a definite number of the cells. To the diluted cell suspension are then added 200 ng/ml of 12-o-tetradodecanoylphorbol-13-acetate (TPA) and the resulting culture medium is then incubated for 20 minutes at 37 °C in the presence of 0.1% of NBT. Thus, the mature differentiated cells containing blue-black formazan are counted by microscope, so that the ratio of the cells having the ability to reduce NBT, to total cells, can be calculated.

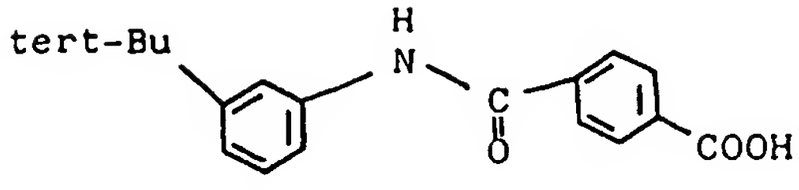
The cells treated with a compound of this invention show an NBT reduction activity which corresponds to the important biochemical activity of differentiated cells.

The results of the tests according to the abovementioned method are summarized in Table 1.

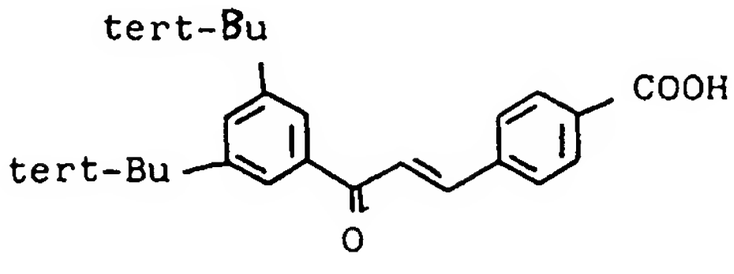
As a positive control for comparison, the known compounds represented by the formula (II) and trans retinoic acid were used.

Table 1

No.	Test Compound	ED_{50} (M)*
	Present compound	
1.		8×10^{-8}
2.		2×10^{-8}
3.		3×10^{-8}
4.		4×10^{-10}
5.		2×10^{-10}
6.		6×10^{-8}
	Reference compound	
7.		1×10^{-7}

8. 

1×10^{-6}

9. 

4×10^{-10}

10. retinoic acid

2×10^{-9}

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*ED_{50}: Effective doses which cause differentiation of 50% of the cultured cells, M(mol/l).

The results shown in Table 1 indicate that the activity of the compound of this invention is equal to or greater than that of known compounds of the formula (II) and retinoic acid. Thus , these compounds are very useful in the determination of promyelocytic leukemia and the diseases which is accompanied by hyperkeratinization or inflammation, such as psoriasis, which enables the selection of a proper therapeutical method of approach.

The following References and Examples are given by way of illustration only and are not to be construed as limitations of this invention.

Reference 1

p-Trimethylgermylacetophenone

a) 2-(4-Trimethylgermylphenyl)-2-methyl-1,3-dioxolane

To a mixture of 108 mg (4.44mmol) of magnesium and 766 mg (5.00mmol) of trimethylgermyl chloride was added a solution of 972 mg (4.00mmol) of 2-(4-bromophenyl)-2-methyl-1,3-dioxolane in 12 ml of dry tetrahydrofuran (THF) at 40 °C with stirring. The mixture was refluxed for 1.5 hours and stirred at room temperature overnight. An insoluble substance was filtered off and washed with ether. The filtrate and washings were mixed and evaporated. The residue was purified by column chromatography on silica gel [eluent: petroleum ether-methylene chloride (2:1-1:2)] and recrystallized from petroleum ether to give 524 mg of white prisms, m.p.63.5-65 °C.

^{1}H-NMR spectrum δ ($CDCl_3$)ppm: 0.38 (9H,s), 1.66 (3H,s), 3.74-3.83 (2H,m), 4.00-4.08 (2H,m), 7.46 (4H,s).

b) p-Trimethylgermylacetophenone

A solution of 420mg (1.5mmol) of 2-(4-trimethylgermylphenyl)-2-methyl-1,3-dioxolane and 56mg (0.19mmol) of pyridinium p-toluenesulfonate (PPTS) in 1.35g (62.5mmol) of water and 10ml of acetone was refluxed for 2 hours and stirred at room temperature for 1.5 days. The reaction mixture was extracted with petroleum ether. The extract was washed successively with 2N hydrochloric acid, water and sat.aq.$NaHCO_3$, dried and evaporated.

The residue was purified by column chromatography on silica gel [eluent: methylene chloride-n-hexane (2:3)] to give 344mg of colorless liquid.

^{1}H-NMR spectrum δ ($CDCl_3$)ppm: 0.41 (9H,s), 2.60 (3H,s), 7.58 (2H,d,J = 8.3Hz), 7.91 (2H,d,J = 8.3Hz).

Reference 2

m-Trimethylsilylaniline

a) 1-Nitro-3-trimethylsilylbenzene
To a solution of 1.50g (6.75mmol) of m-bis(trimethylsilyl)benzene in 4.0ml of acetic anhydride was added dropwise a solution of 1.6ml (35.6mmol) of 94% nitric acid in 5ml of acetic anhydride at 130 • C with stirring. The mixture was stirred for 30 minutes. The reaction mixture was poured into a mixture of ice and 2% potassium carbonate solution and methylene chloride and separated. The aqueaus layer was extracted with methylene chloride. The organic layer was washed successively with water and 2% potassium hydroxide solution, dried and evaporated. The residue was purified by column chromatogaphy on silica gel [eluent: methylene chloride-cyclohexane (1:3-1:5)] to give 475mg of pale yellow liquid.
^{1}H-NMR spectrum δ ($CDCl_3$)ppm: 0.35 (9H,s), 7.50 (1H,t,J = 8Hz), 7.81 (1H,d,J = 8Hz), 8.15 (1H,d,J = 8Hz), 8.32 (1H,s).
b) m-Trimethylsilylaniline
m-Nitrotrimethylsilylbenzene (200mg) was catalytically hydrogenated over Pd-C in 7.5ml of benzene at atmospheric pressure for 40 minutes. The catalyst was filtered off and washed with benzene and dry MeOH, successively. The filtrate and washings were mixed and evaporated. The residue was purified by column chromatography on silica gel [eluent: methylene chloride] to give 169mg of pale brown liquid.
^{1}H-NMR spectrum δ ($CDCl_3$)ppm: 0.26 (9H,s), 3.61 (2H,s), 6.6-7.0 (3H,m), 7.16 (1H,t,J = 8Hz).

Example 1

4-(3-Trimethylsilylphenylcarbamoyl)benzoic Acid

a) Methyl 4-(3-Trimethylsilylphenylcarbamoyl)benzoate
To a solution of 135mg (0.817mmol) of m-trimethylsilylaniline in 8ml of dry benzene were added 1.0ml of dry pyridine and 179mg (0.900mmol) of methyl p-chloroformylbenzoate, successively. The mixture was stirred at room temperature for 20 hours. To the reaction mixture was added water and the aqueous solution was extracted with AcOEt. The extract was washed successively with water, sat.eq.$NaHCO_3$ and sat.aq.NaCl, dried and evaporated to give 272mg of white powder, which was purified by column chlomatography on silica gel (eluent: methylene chloride) to give 266mg of white powder (yield: 99%). Recrystallization of the powder from a mixture of methylene chloride, n-hexane and chloroform gave 120mg of white needles, m.p.125-126 • C (yield 45%).
MS spectrum m/z: 327(M^+), 312(M^+-15).
^{1}H-NMR spectrum δ($CDCl_3$)ppm: 0.28 (9H,s), 3.96 (3H,s), 7.3-7.8 (5H,m), 7.98 (2H,d,J = 8Hz), 8.13 (2H,d,J = 8Hz).
b) 4-(3-Trimethylsilylphenylcarbamoyl)benzoic Acid
To a solution of 82mg (0.25mmol) of methyl 4-(3-trimethyl-silylphenylcarbamoyl)benzoate in 2ml of EtOH was added 1ml (2mmol) of 2N sodium hydroxide solution and the mixture was stirred at room temperature for 4 hours. The reaction mixture was neutralized with 1N hydrochloric acid and extracted with AcOEt. The extract was washed sucessively with hydrochloric acid and sat.aq.NaCl, dried and evaporated. The residue was recrystallized from MeOH to give 48mg of white prisms,
m.p.211-213 • C (yield 61%).
MS spectrum m/z: 313(M^+), 298(M^+-15), 149($O^+ = C\text{-}C_6H_4\text{-}COOH$).
IR spectrum ν cm^{-1} : 1694, 1669 .
^{1}H-NMR spectrum δ ($CDCl_3$-DMSO-d_6)ppm: 0.29 (9H,s), 7.3-7.8 (4H,m), 8.05 (2H,d,J = 8Hz), 8.13 (2H,d,J = 8Hz), 9.66 (1H,br).
High resolution mass spectrum for $C_{17}H_{19}NO_3Si$:

Calculated m/z	313.1133.
Found m/z	313.1164.

Reference 3

3,5-Bis(trimethylsilyl)aniline

a) 1-Nitro-3,5-bis(trimethylsilyl)benzene
To a solution of 1.18g (4.00mmol) of sym-tris(trimethylsilyl)benzene in 1.7ml of acetic anhydride was added a solution of 0.4ml (9.1mmol) of 94% nitric acid in 1.7ml of acetic anhydride at -10°C. The mixture was stirred at 10 to -5°C for 2 hours and then at room temperature for 22 hours. The reaction mixture was poured into sodium hydroxide solution and the aqueous solution was extracted with methylene chloride. The extract was evaporated. The residue was purified by column chromatography on silica gel [eluent: petroleum ether] to give 636mg of pale yellow crystals, m.p.86-87°C (yield 59%).
^{1}H-NMR spectrum δ ($CDCl_3$)ppm: 0.33 (18H,s), 7.90 (1H,t,J=1.1Hz), 8.29 (2H,d,J=1.1Hz).
b) 3,5-Bis(trimethylsilyl)aniline
1-Nitro-3,5-bis(trimethylsilyl)benzene (264mg, 0.99mmol) was catalytically hydrogenated over 10% Pd-C in 15ml of benzene at atmospheric pressure for 135 minutes. The catalyst was filtered off and washed with benzene. The filtrate and washings were mixed and evaporated. The residue was purified by column chromatography on silica gel [eluent: methylene chloride-n-hexane (2:1)] to give 224mg of light tan-colored low melting solid (yield 96%).
^{1}H-NMR spectrum δ ($CDCl_3$)ppm: 0.24 (18H,s), 3.36 (2H,brs), 6.84 (2H,brs), 7.07 (1H,brs).

Example 2

4-(3,5-Trimethylsilylphenylcarbamoyl)benzoic Acid

a) Methyl 4-(3,5-Trimethylsilylphenylcarbamoyl)benzoate
To a solution of 220mg (0.93mmol) of 3,5-bis(trimethylsilyl)aniline and 187mg (0.94mmol) of methyl p-chloroformylbenzoate in 10ml of dry benzene was added 1ml of dry pyridine. The mixture was stirred for 5.75 hours. Water was added to the reaction mixture and the aqueous layer was extracted with AcOEt. The extract was washed with 0.2M aqueous copper nitrate solution, water and sat.aq.$NaHCO_3$, successively, dried and evaporated. The residue was recrystallized from a mixture of methylene chloride and n-hexane to give 352mg of white prisms, m.p.212.5-213.5°C (yield 95%).
^{1}H-NMR spectrum δ ($CDCl_3$)ppm: 0.30 (18H,s), 3.97 (3H,s), 7.46 (1H,t,J=1.1Hz), 7.76 (2H,d,J=1.1Hz), 7.79 (1H,brs), 7.96 (2H,d,J=8.4Hz), 8.17 (2H,d,J=8.4Hz).
b) 4-(3,5-Trimethylsilylphenylcarbamoyl)benzoic Acid
To a solution of 300mg (0.75mmol) of methyl 4-(3,5-trimethylsilylphenylcarbamoyl)benzoate in 5ml of EtOH was added 3ml of 2N sodium hydroxide solution and the mixture was stirred at room temperature overnight. The pH of the reaction mixture was adjusted to 3.0 with 2N hydrochloric acid. The aqueous solution was extracted with AcOEt. The extract was dried and evaporated. The white residue was recrystalized from a mixture of AcOEt and cyclohexane and washed with n-hexane to give 255mg of white needles, m.p. 252-253.5°C (yield 88%).
^{1}H-NMR spectrum δ ($CDCl_3$)ppm: 0.30 (18H,s), 7.46 (1H,t,J=1.1Hz), 7.77 (2H,brs), 7.80 (1H,brs), 7.99 (2H,d,J=8.1Hz), 8.21 (2H,d,J=8.1Hz)
High resolution mass spectrum for $C_{20}H_{27}NO_3Si_2$:

Calculated m/z	385.1528.
Found m/z	385.1505.

Reference 4

3,5-Bis(trimethylsilyl)benzoic Acid

A suspension of 2.0g (14mmol) of $Ca(OCl)_2$, 1.38g(10mmol) of potassium carbonate and 0.40g (7.12mmol) of potassium hydroxide in 40ml of water was stirred at 65°C for 30 minutes and filtered. The filtrate was added to 0.53g (2mmol) of 3',5'-bis(trimethylsilyl)acetophenone and the mixture was refluxed for 7.5 hours with stirring. After cooling, 3ml of aqueous sodium bisulfite solution was added to the reaction mixture. The aqueous solution was extracted with AcOEt. The extract was washed successively with water

and sat.aq.NaCl, dried over anhyd.Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel [eluent: n-hexane-AcOEt (2:1-1:1)] to give 0.27g of white powder, m.p.>300°C (yield 51%).
MS spectrum m/z: 266 (M^+).
^{1}H-NMR spectrum δ ($CDCl_3$)ppm: 0.32 (18H,s), 7.88 (1H,t,J = 1.1Hz), 8.24 (2H,d,J = 1.1Hz).

Exanmple 3

4-[3,5-Bis(trimethylsilyl)phenylcarboxamido]benzoic Acid

a) Methyl 4-[3,5-Bis(trimethylsilyl)phenylcarboxamido]benzoate
To a suspension of 1.064g (4mmol) of 3,5-bis(trimethylsilyl)benzoic acid and 1.05g of potassium carbonate in 104ml of dry benzene were added 0.64ml (8.8mmol) of thionyl chloride and 0.34ml (4.4mmol) of N,N-dimethylformamide (DMF) at room temperature with stirring. The mixture was stirred at room temperature for 3 hours and the insoluble substance was filtered off. The filtrate was evaporated and the residue was dissolved in 25ml of dry tetrahydrofuran. To the solution were added 1.23ml (8.8mmol) of triethylamine and 0.665g (4.4mmol) of methyl p-aminobenzoate and the mixture was stirred at room temperature overnight. The reaction mixture was made weakly acid with 0.5N hydrochloric acid and extracted with methylene chloride.
The extract was successively washed with water and sat.aq.NaCl, dried over anhyd.Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel (eluent: n-hexane-AcOEt (5:1)) to give 1.34g of pale yellow crystals, m.p.191-192°C (yield 84%).
MS spectrum m/z: 399 (M^+)
^{1}H-NMR spectrum δ ($CDCl_3$) ppm: 0.31 (18H,s), 3.90 (3H,s), 7.74 (2H,d,J = 8.8Hz), 7.83 (1H,t,J = 1.1Hz), 7.96 (2H,d,J = 1.1Hz), 8.04 (2H,d,J = 8.8Hz), 8.14 (1H, br.s).
b) 4-[3,5-Bis(trimethylsilyl)phenylcarboxamido]benzoic Acid To a solution of 22mg(0.055mmol) of methyl 4-[3,5-bis(trimethylsilyl)phenylcarboxamido]benzoate in 6ml of EtOH was added 3ml of 2N aqueous sodium hydroxide solution and the mixture was stirred at room temperature overnight. The reaction mixture was made weakly acid with hydrochloric acid and extracted with AcOEt. The extract was washed with sat.aq.NaCl, dried over $MgSO_4$ and evaporated. The residue was recrystallized from a mixture of AcOEt and n-hexane to give 14mg of colorless prisms, m.p.276-280°C (dec.) (yield 66%).
MS spectrum m/z : 385 (M^+)
^{1}H-NMR spectrum δ ($CDCl_3$) ppm: 0.33 (18H,s), 7.78 (2H,d,J = 8.8Hz), 7.84 (1H,br.s), 7.94 (2H,d,J = 0.9Hz), 8.14 (2H,d,J = 8.8Hz).

Example 4

Methyl 4-[3,5-Bis(trimethylsilyl)phenylcarboxy]benzoate

To a suspension of 665mg (2.5mmol) of 3,5-bis(trimethylsilyl)bonzoic acid and 670mg of potassium carbonate in dry benzene were added 0.40ml (5.5mmol) of thionyl chloride and 0.21ml (2.75mmol) of N,N-dimethylformamide at room temperature with stirring. The mixture was stirred at room temperature for 3 hours. The insoluble matter was filtered off and the filtrate was evaporated. The residue was dissolved in 17.5ml of dry tetrahydrofuran and 0.77ml(5.5mmol) of triethylamine and 418mg (2.75mmol) of methyl p-hydroxybonzoate were added to the solution. The mixture was stirred at room temperature for 1 day. The reaction mixture was made weakly acid with hydrochloric acid and extracted with methylene chloride. The extract was successively, washed with water and sat.aq.NaCl, dried over anhyd.Na_2SO_4 and evaporated.
The residue was purified by column chromatography on silica gel [eluent:n-hexane-AcOEt (10:1)] to give 930mg of white crystals (yield 93%), which was recrystalized from an aqueous methanol to give 790mg of colorless needles, m.p. 81-82°C (yield 79%).
MS spectrum m/z : 400(M^+), 385(M^+-15).
^{1}H-NMR spectrum δ ($CDCl_3$) ppm:0.33 (18H,s), 3.93 (3H,s), 7.30 (2H,d,J = 8.8Hz), 7.91 (1H,t,J = 0.9Hz), 8.13 (2H,d,J = 8.8Hz), 8.30 (1H,d,J = 0.9Hz).

Example 5

4-[(3-Trimethylsilylphenyl)ethenyl]benzoic Acid

a) (m-Trimethylsilylbenzyl)phosphonium Bromide A solution of 730mg (3.00mmol) of m-trimethylsilylbenzyl bromide and 1.18g (4.50mmol) of triphenylphosphine in 10ml of dry toluene was refluxed for 4.5hours in an atmosphere of argon (125-135•c by oil bath). The precipitate was collected by filtration, and washed with toluene to give 1.361g of white crystals, which were dried in vacuo (yield 90%).
^{1}H-NMR spectrum δ (CD_3OD)ppm: 0.30 (9H,S), 5.13 (2H,d,J = 16Hz), 7.1-8.1 (19H,m).

b) Methyl 4-[(3-Trimethylsilylphenyl)ethenyl]benzoate
(m-Trimethylsilylbenzyl)phosphonium bromide (758mg,1.50mmol) and methyl 4-formylbenzoate (258mg,1.57mmol) were added to a NaOMe-methanol solution, which was prepared from 40mg (1.74mmol) of Na metal and 15ml of dry methanol, and the mixture was stirred for 17 hours. The precipitate (trans form) was collected by filtration, washed with a cooled mixture of MeOH and n-hexane,and dried in vacuo to give 115mg of white crystals. The mother liquors were evaporated and dissolved in CH_2Cl_2. The insoluble substance was filtered off and the filtrate was evaporated. The residue was purified by column chromatography to give 60mg of colorless oil (cis form, yield 13%), 158mg of white crystals (trans form, total yield 59%) and 110mg of interfraction (yield 23%).

The trans form was recrystallized from a mixture of CH_2Cl_2 and n-hexane to give 149mg of white needles. The mother liquors were evaporated. The residue was recrystallized from n-hexane to give 120mg of white needles (total 269mg, yield 58%).
m.p.113-114.5•C
^{1}H-NMR spectrum δ ($CDCl_3$)ppm: 0.30 (9H,s), 3.92 (3H,m), 7.0-7.6 (8H,m), 8.02 (2H,d,J = 8Hz).
Mass spectrum m/z: 310 (M^+), 295 (M^+-15).
IR spectrum ν cm^{-1} : 1723, 1282, 1250.
UV spectrum λ_{max} nm(log ϵ): 323 (4.91), 232 (4.61), 209 (4.75).

The physical properties of the cis form were as follows.
^{1}H-NMR spectrum δ ($CDCl_3$)ppm: 0.16 (9H,s), 3.90 (3H,s), 6.59 (1H,d,J = 12Hz), 6.69 (1H,d,J = 12Hz), 7.1-7.4 (6H,m), 7.87 (2H,d,J = 8Hz).
IR spectrum ν cm^{-1}: 1724, 1280, 1250.
UV spectrum λ_{max} nm(log ϵ): 303 (3.97), 237 (4.19), 203 (4.24).

(c) 4-[(3-Trimethylsilylphenyl)ethenyl]benzoic Acid
A solution of 1.8ml(3.6mmol) of 2N-KOH was added to a solution of 143mg (0.461mmol) of trans-methyl 4-[(3-trimethylsilylphenyl)ethenyl]benzoate in 3ml of EtOH. The mixture was stirred at room temperature. The reaction mixture was adjusted to pH with 2N hydrochloric acid, and then the aqueous solution was extracted with AcOEt. The extract was dried and evaporated to give 137mg of the title compound as white crystals (yield 100%), which were recrystallized from a mixture of ethyl acetate, methylene chloride and n-hexane, and dried to give 116mg of white crystals, m.p.216-218•C (yield 85%).
^{1}H-NMR spectrum δ ($CDCl_3$-DMSO-d_6)ppm: 0.30 (9H,s), 7.12 (1H,d,J = 18Hz), 7.25 (1H,d,J = 18Hz), 7.4-7.8 (6H,m), 7.95 (2H,d,J = 8Hz).
IR spectrum ν cm^{-1}: 1670.
High resolution mass spectrum for $C_{18}H_{20}O_2Si$:

Calculated m/z	296.1232.
Found m/z	296.1250.

Example 6

4-[3-(3-Trimethylsilylphenyl)-3-oxo-1-propenyl]benzoic Acid

To a solution of 130mg (0.676mmol) of 3'-trimethylsilylacetophenone and 127mg (0.774mmol) of methyl 4-formylbenzoate in 4.5ml of tetrahydrofuran(THF) were added 128mg (3.20mmol) of NaOH and 3ml of hot water, and the mixture was stirred at room temperature overnight. The reaction mixture was adjusted with 7ml of 0.5N-HCl to pH6, and then the aqueous solution was extracted with ethyl acetate. The extract was washed with 0.05N-HCl and H_2O, dried and evaporated. The residue was purified by column chromatography affording 133mg of pale yellow powder (yield 61%), which was recrystallized from a mixture of

methylene chloride, methanol and n-hexane to give 98mg of pale yellow needles, m.p.179-180 • C (yield 45%).
^{1}H-NMR spectrum δ ($CDCl_3$)ppm: 0.33 (9H,s), 7.51 (1H,t,J = 7.7Hz), 7.62 (1H,d,J = 15.8Hz), 7.74 (2H,d,J = 8.1Hz), 7.76 (1H,d,J = 7.7Hz), 7.82 (1H,d,J = 15.8Hz), 7.99 (1H,d,J = 7.7Hz), 8.14 (2H,d,J = 8.1Hz), 8.15 (1H,m).

Example 7

4-[3-(3,5-Bistrimethysilylphenyl)-3-oxo-1-propenyl]benzoic Acid

Under ice-cooling, to a solution of 114mg (0.43mmol) of 3',5'-bis(trimethylsilyl)acetophenone and 70mg (0.43mmol) of methyl 4-formylbenzoate in 3ml of THF was added a solution of 40 mg (1.00mmol) of NaOH in 2ml of H_2O with stirring, and the mixture was stirred in an atmosphere of prepurified argon overnight. The reaction mixture was further added to 39mg of NaOH, stirred for 2 days, and then the solution was adjusted with 2N-HCl to pH≦7 and extracted with ethyl acetate. The extract was dried and evaporated. The residue was purified by column chromatography using methylene chloride-methanol (10:1) as an eluant to give 112mg of the desired compound (yield 66%), which was recrystallized from a mixture of ethyl acetate and n-hexane to give 98mg of pale yellow prisms, m.p.194-195.5 • C (yield 57%).
^{1}H-NMR spectrum δ ($CDCl_3$)ppm: 0.33 (18H,s), 7.59 (1H,d,J = 15.7Hz), 7.73 (2H,d,J = 8.1Hz), 7.80 (1H,d,J = 15.7Hz), 7.87 (1H,t,J = 1.1Hz), 8.10 (2H,d,J = 1.1Hz), 8.16 (2H,d,J = 8.1Hz),
High resolution mass spectrum for $C_{22}H_{28}O_3Si_2$:

Calculated m/z	396.1575.
Found m/z	396.1558.

Reference 5

3'-Trimethylgermylacetophenone

a) 2-(3-Trimethylgermylphenyl)-2-methyl-1,3-dioxolane
A mixture of 81mg (3.33mmol) of magnesium and 574mg (3.75mmol) of trimethylgermyl chloride was stirred at 40-50 • C in an atmosphere of argon. To the mixture was added a solution of 729mg (3.00mmol) of 2-(3-bromophenyl)-2-methyl-1,3-dioxolane in 10ml of tetrahydrofuran with stirring. The mixture was refluxed for 2.5hr. and stirred at room temperature overnight. To the reaction mixture was added petroleum ether and the insoluble substance was filtered off. The filtrate was evaporated to give 874mg of pale yellow crystals, which were purified by column chromatography on silica gel [eluent: methylene chloride-n-hexane (1:1)] to give 657mg of white cubes, m.p.62.5-63.5 • C (yield 78%).
^{1}H-NMR spectrum δ ($CDCl_3$)ppm: 0.39 (9H,s), 1.67 (3H,s), 3.75-3.83 (2H,m), 4.00-4.09 (2H,m),7.33 (1H,t,J = 7.4Hz), 7.41 (1H,dt,J = 7.4,1.3Hz), 7.44 (1H,ddd,J = 7.4,1.9,1.3Hz), 7.58 (1H,m).
^{13}H-NMR spectrum δ ($CDCl_3$)ppm: -1.76, 27.71, 64.42, 108.98, 125.24, 127.66, 129.50, 132.43, 142.53, 142.56
b) 3'-Trimethylgermylacetophenone A mixture of 351mg (1,25mmol) of 2-(3-trimethylgermylphenyl)-2-methyl-1,3-dioxolane, 47mg (0.187mmol, 0.15eq) of pyridinium p-toluenesulfonate (PPTS), 1.1126g (62.5mmol, 50eq) of water and 10ml of acetone was refluxed for 2.5hours. The reaction mixture was evaporated and extracted with petroleum ether. The extract was evaporated. The oily residue was purified by column chromatography to give 294mg of colorless oily substance.
^{1}H-NMR spectrum δ ($CDCl_3$)ppm: 0.42 (9H,s), 2.62 (3H,s), 7.44 (1H,ddd,J = 7.7,7.3,0.6Hz), 7.67 (1H,dt,J = 7.3,1.3Hz), 7.90 (1H,ddd,J = 7.7,1.9,1.3Hz), 8.06 (1H,ddd,J = 1.9,1.3,0.6Hz)

Example 8

4-[3-(3-Trimethylgermylphenyl)-3-oxo-1-propenyl]benzoic Acid

3'-Trimethylgermylacetophenone (49mg,0.2mmol) and methyl 4-formylbenzoate (37mg,0.23mmol) was dissolved in 5ml of a mixture of 50% isopropanol and tetrahydrofuran, 1ml of 1N aqueous potassium hydroxide solution was added, and the mixture was stirred overnight. The reaction mixture was adjusted to

pH1 with 2N hydrochloric acid and extracted with AcOEt. The extract was evaporated and the residue was purified by column chromatography on silica gel (eluent: MeOH-methylene chloride) and recrystallized from a mixture of AcOEt and n-hexane to give 17mg of pale yellow prisms, m.p.186-188 • C (yield 22%).
^{1}H-NMR spectrum δ ($CDCl_3$)ppm: 0.45 (9H,s), 7.50 (1H,dd,J = 7.9,7.3Hz), 7.62 (1H,d,J = 15.8Hz), 7.72 (1H,dt,J = 7.3,1.3Hz), 7.74 (1H,d,J = 8.4Hz), 7.83 (1H,d,J = 15.8Hz), 8.11 (1H,m), 8.14(1H,d,J = 8.4Hz).

Reference 6

3'5'-Bis(trimethylgermyl)acetophenone

a) 2-(3,5-Bis(trimethylgermyl)phenyl]-2-methyl-1,3-dioxolane and 2-(3-Trimethylgermyl)-2-methyl-1,3-dioxolane
To a suspension of 108mg (4.44 mmol) of magnesium and 765mg (5.00mmol) of trimethylgermyl chloride was added a solution of 644mg (2.00mmol) of 2-(3,5-dibromophenyl)-2-methyl-1,3-dioxolane in 10 ml of tetrahydrofuran at 40 • C, stirred in an atmosphere of argon. The mixture was stirred at 70 • C for 4.5hr. and at room temperature overnight. The reaction mixture was poured into ice-aqueous sodium bicarbonate solution and extracted with methylene chloride. The solvent was removed to give pale brown crystals, which were purified by column chromatography on silica gel [eluent: methylene chloride-n-hexane (1:1)] to give 514mg (yield 65%) of
2-(3,5-bis(trimethylgermyl)phenyl]-2-methyl-1,3-dioxolane, m.p.54 • C, and 61mg (yield 11%)of
2-(3-trimethylgermylphenyl)-2-methyl-1,3-dioxolane and 75mg of the mixture, in which ratio was 3:2 (by NMR).

The physical properties of 2-(3,5-bis(trimethylgermyl)phenyl]-2-methyl-1,3-dioxolane were as follows:
^{1}H-NMR spectrum δ ($CDCl_3$)ppm: 0.39 (18H,s), 1.68 (3H,s), 3.76-3.83 (2H,m) 4.01-4.10 (2H,m), 7.50 (1H,t,J = 1.1Hz), 7.55 (2H,d,J = 1.1Hz)
The physical properties of
2-(3-trimethylgermylphenyl)-2-methyl-1,3-dioxolane were as follows.
^{1}H-NMR spectrum δ ($CDCl_3$)ppm: 0.39 (9H,s), 1.67 (3H,s), 3.75-3.84 (2H,m), 4.00-4.09 (2H,m), 7.33 (1H,t,J = 7.3Hz), 7.41 (1H,ddd,J = 7.3,1.5,1.1Hz), 7.44 (1H,ddd,J = 7.3,1.8,1.5Hz), 7.58 (1H,m).

b)3',5'-Bis(trimethylgermyl)acetophenone
A mixture of 240mg (0.60mmol) of 2-[3,5-bis(trimethylgermyl)phenyl]-2-methyl-1,3-dioxolane, 23mg (0.090mmol) of PPTS, 10.6ml of acetone (excess) and 540mg (30mmol) of water was refluxed for 2.5hours. The reaction mixture was evaporated and extracted with ether. The extract was evaporated to give 208mg of pale yellow crystals, which were sublimed at 70 • C, 0.5mmHg to give 189mg of white prisms, m.p.56 • C (yield 89%).
^{1}H-NMR spectrum δ ($CDCl_3$)ppm: 0.43 (18H,s), 2.63 (3H,s), 7.74 (1H,t,J = 1.1Hz), 7.99 (2H,d,J = 1.1Hz).
IR spectrum ν cm^{-1}: 1986.

Example 9

4-[3-(3,5-Bistrimethylgermylphenyl)-3-oxo-1-propenyl]benzoic Acid

3',5'-Bis(trimethylgermyl)acetophenone 163mg (0.46mmol) and 96mg (0.58mmol) of methyl 4-formyl-benzoate was dissolved in 4ml of a mixture of isopropanol and tetrahydrofuran (1:1). To the mixture was added 2.5ml of 0.75N aqueous potassium hydroxide solution with stirring and the mixture was stirred at room temperature overnight. The reaction mixture was adjusted to pH3.8 with 0.2N hydrochloric acid and extracted with AcOEt. The extract was evaporated. The residue was purified by column chromatography on silicagel [eluent: methylene chloride-MeOH (10:1)] and recrystallized from a mixture of methylene chloride, MeOH and n-hexane to give 120mg of yellow prisms, m.p.194-195.5 • C (dec.).
^{1}H-NMR spectrum δ ($CDCl_3$)ppm: 0.45 (18H,s), 7.59 (1H,d,J = 15.8Hz), 7.74 (2H,d,J = 8.3Hz), 7.78 (1H,t,J = 1.1Hz), 7.81 (1H,d,J = 15.8Hz), 8.03 (2H,d,J = 1.1Hz),8.16 (2H,d,J = 8.3Hz).

Analysis for $C_{22}H_{28}O_3Ge_2$:			
Calculated	C,54.41;	H,5.81;	N,0.
Found	C,54.57;	H,5.94;	N,0.

Reference 7

2'-Hydroxy-5'-trimethylsilylacetophenone

a) 2-(2-Trimethylsilyloxy-5-bromophenyl)-2-methyl-1,3-dioxolane
Under ice-cooling, to a solution of 3.11g (12mmol) of 2-(2-hydroxy-5-bromophenyl)-2-methyl-1,3-dioxolane in 24ml of tetrahydrofuran was added dropwise succesively, 1.84ml (13.2mmol) of triethylamine and 1.68ml (13.2mmol) of trimethylsilyl chloride with stirring. The mixture was stirred at room temperature for 2hours and filtered. The filtrate was concentrated under reduced pressure to give 4.0g of the crude product.
b) 2'-Hydroxy-5'-trimethylsilylacetophenone
A mixture of 321mg (13.2mmol) of magnesium, 0.07ml of ethyl iodide and 1.32ml of dry tetrahydrofuran was refluxed. After cooling, the mixture was diluted with 3.96ml of dry tetrahydrofuran and refluxed. To the mixture was added dropwise a solution 4.0g of crude
2-(2-trimethylsilyloxy-5-bromophenyl)-2-methyl-1,3-dioxolane, obtained as above, in 9.6ml of tetrahydrofuran and the reaction mixture was refluxed for 2hours. After cooling, 1.68ml (13.2 mmol) of trimethylsilyl chloride was added and refluxed for 3hours. Water was added to the reaction mixture. The mixture was extracted with ether. The extract was washed with water and sat.aq.NaCl, dried over anhyd.Na_2SO_4 and evaporated. To the residue was added 72ml of acetone, 10.8ml (600mmol) of water and 0.46g (1.8mmol) of PPTS. The mixture was refluxed for 3 hours and evaporated. The residue was dissolved in ether. The solution was washed with water, aqueous sodium bicarbonate solution and sat.aq.NaCl, dried over anhyd.Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel [eluent: n-hexane-AcOEt (20:1)] to 1.66g of pale yellow liquid (yield 67%).
MS spectrum m/z: 208(M^+), 193(M^+-15).
^{1}H-NMR spectrum δ ($CDCl_3$)ppm: 0.28 (9H,s), 2.65 (3H,s), 6.96 (1H,d,J=7.9Hz), 7.59 (1H,dd,J=7.9,1.8Hz), 7.84 (1H,d,J=1.8Hz) 12.31 (1H,s).

Example 10

4-[1-Hydroxy-3-(2-hydroxy-5-trimethylsilylphenyl)-3-oxo-1-propenyl]benzoic Acid

a) 2-Acetyl-4-trimethylsilylphenyl Methyl 1,4-Benzenedicarboxylate
Under ice-cooling, to a solution of 832mg (4mmol) of 2'-hydroxy-5'-timethylsilylacetophenone in 20ml of tetrahydrofuran were added dropwise successively, 0.61ml (4.4mmol) of triethylamine and 874mg (4.4mmol) of methyl p-chloroformylbenzoate with stirring. The mixture was stirred at room temperature for 1 day and filtered. The filtrate was evaporated and the residue was dissolved in AcOEt. The organic solution was washed with H_2O, aqueous sodium bicarbonate solution and brine, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel [eluent: n-hexane-AcOEt (5:1)] to give 1.25g of white crystals (yield 85%), m.p.88.5-90.5 °C.
MS spectrum m/z: 370 (M^+).
^{1}H-NMR spectrum δ ($CDCl_3$)ppm: 0.32 (9H,s), 2.55 (3H,s), 3.97 (3H,s), 7.22 (1H,d,J=7.7Hz), 7.73 (1H,dd,J=7.7,1.5Hz), 7.97 (1H,d,J=1.5Hz), 8.16 (2H,d,J=8.8Hz), 8.29 (2H,d,J=8.8Hz).
b) Methyl 4-[1-Hydroxy-3-(2-hydroxy-5-trimethylsilylphenyl)-3-oxo-1-propenyl]benzoate
To a solution of 740mg (2mmol) of 2-acetyl-4-trimethylsilylphenyl methyl 1,4-benzenedicarboxylate in 14ml of pyridine was added 280 mg (5mmol) of ground potassium hydroxide at room temperature with stirrig. The mixture was stirred at room temperatre overnight and poured into a chilled 20%-aqueous solution of acetic acid. A deposited precipitation was extracted with AcOEt. The extract was washed with H_2O and saturated aq.NaCl, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel [eluent: n-hexane-AcOEt (5:1)] to give 200mg of yellow crystals (yield 27%), m.p.129.5-131 °C .
MS spectrum m/z: 370 (M^+).
^{1}H-NMR spectrum δ ($CDCl_3$)ppm: 0.31 (9H,s), 3.96 (3H,s), 6.88 (1H,s), 7.00 (1H,d,J=7.9Hz), 7.61 (1H,dd,J=7.9,1.3Hz), 7.85 (1H,d,J=1.3Hz), 7.97 (2H,d,J=8.8Hz), 8.17 (2H,d,J=8.8Hz), 12.04 (1H,s), 15.44 (1H,s).
c) 4-[1-Hydroxy-3-(2-hydroxy-5-trimethylsilylphenyl)-3-oxo-1-propenyl]benzoic Acid
To a solution of 148 mg (0.4mmol) of methyl
4-[1-hydroxy-3(2-hydroxy-5-trimethylsilylphenyl)-3-oxo-1-propenyl] benzoate in 20ml of ethanol was added 2ml of 2N-sodium hydroxide solution at room temperature with stirring. The mixture was stirred at

room temperature for 1 day and acidified with 10%-hydrochloric acid to pH 4. A deposited precipilation was extracted with AcOEt. The extract was washed with H_2O and saturated aq.NaCl, dried over $MgSO_4$, and evaporated. The residue was recrystallized from methanol to give 72mg of yellow needles (yield 51%), m.p.207-209 • C.
MS spectrum m/z: 356 (M^+).
^{1}H-NMR spectrum δ (DMSO-d_6)ppm: 0.26 (9H,s), 6.84-8.30 (8H,m).

Reference 8

2'-Hydroxy-4'-trimethylsilylacetophenone

a) 2-(4-Bromo-2-trimethylsilyloxyphenyl)-2-methyl-1,3-dioxolane
Under ice-cooling, to a solutin of 3.11g (12mmol) of 2-(2-hydroxy-4-bromophenyl)-2-methyl-1,3-dioxolane in 24ml of tetrahydrofuran were added dropwise successively, 1.84ml (13.2mmol) of triethylamine and 1.68ml (13.2mmol) of trimethylsilyl chloride with stirring. The mixture was stirred at room temperature for 3 hours and filtered. The filtrate was concentrated under reduced pressure to give 4.0g of the crude product.
b) 2'-Hydroxy-4'-trimethylsilylacetophenone
A mixture of 321mg (13.2mmol) of magnesium and 0.07ml of methyl iodide in 1.32ml of dry tetrahydrofuran was refluxed. After cooling, the mixture was diluted with 3.96 ml of dry tetrahydrofuran. To the mixture was added a solution of 4.0g of crude 2-(4-bomo-2-trimethylsilyloxyphenyl)-2-methyl-1,3-dioxolane obtained above in 9.6ml of dry tetrahydrofuran dropwise under refluxing and the mixture was refluxed for additional 2 hours. After cooling, 1.68ml (13.2mmol) of trimethylsilyl chloride was added to the reaction mixture and the mixture was refluxed for 2 hours. After cooling, water was added to the reaction mixture. The mixture was extracted with ether. The organic layer was washed with H_2O and brine, dried over anhydrous Na_2SO_4, and evaporated. To the residue were added 72ml of acetone, 10.8ml (600mmol) of water and 0.46g (1.8mmol) of pyridinium p-toluenesulfonate (PPTS). The mixture was refluxed for 4 hours, neutralized with aqueous sodium bicarbonate solution, and evaporated. The residue was dissolved in ether. The solution was washed with water, sodium bicarbonate and brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel [eluent: n-hexane-AcOEt (15:1)] to give 1.08g of pale yellow liquid (yield 43%).
MS spectrum m/z: 208 (M^+), 198 (M^+-15).
^{1}H-NMR spectrum δ ($CDCl_3$)ppm: 0.27 (9H,s), 2.63 (3H,s), 7.03 (1H,dd,J=7.9,1.3Hz), 7.14 (1H,d,J=1.3Hz), 7.69 (1H,d,J=7.9Hz), 12.15 (1H,s).

Example 11

4-[1-Hydroxy-3-(2-hydroxy-4-trimethylsilylphenyl)-3-oxo-1-propenyl]benzoic Acid

a) 2-Acetyl-5-trimethylsilylphenyl Methyl 1,4-Benzenedicarboxylate
Under ice-cooling, to a solution of 832mg (4mmol) of 2'-hydroxy-4'-timethylsilylacetophenone in 20ml of tetrahydrofuran were added dropwise successively, 0.61ml (4.4mmol) of triethylamine and 874mg (4.4mmol) of methyl p-chloroformylbenzoate with stirring. The mixture was stirred at room temperature for 1 day and filtered. The filtrate was evaporated and the residue was dissolved in AcOEt. The organic solution was washed with H_2O, aqueous sodium bicarbonate solution and brine, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel [eluent: n-hexane-AcOEt (5:1)] to give 1.40g of pale yellow viscous liquid (yield 95%).
MS spectrum m/z: 370 (M^+).
^{1}H-NMR spectrum δ ($CDCl_3$)ppm: 0.31 (9H,s), 2.54 (3H,s), 3.98 (3H,s), 7.34 (1H,d,J=1.1Hz), 7.51 (1H,dd,J=7.5,1.1Hz), 7.84 (1H,d,J=7.5Hz), 8.16 (2H,d,J=9.0Hz), 8.30 (2H,d,J=9.0Hz).
b) Methyl 4-[1-Hydroxy-3-(2-hydroxy-5-trimethylsilylphenyl)-3-oxo-1-propenyl]benzoate
To a solution of 740mg (2mmol) of 2-acetyl-4-trimethylsilylphenyl methyl 1,4-benzenedicarboxylate in 14ml of pyridine was added 280 mg (5mmol) of ground potassium hydroxide with stirring under ice-cooling. The mixture was stirred at same temperature for 1.5 hours and poured into a chilled 20%-aqueous solution of acetic acid. A deposited precipitation was extracted with AcOEt. The extract was washed with H_2O and brine, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel [eluent: n-hexane-AcOEt (5:1)] to give 510mg of yellow crystals (yield 69%), m.p.152-154 • C .

MS spectrum m/z: 370 (M^+).

^{1}H-NMR spectrum δ ($CDCl_3$)ppm: 0.29 (9H,s), 3.96 (3H,s), 6.89 (1H,s), 7.06 (1H,dd,J=7.9,0.9Hz), 7.17 (1H,d,J=0.9Hz), 7.73 (1H,d,J=7.9Hz), 7.97 (2H,d,J=8.8Hz), 8.15 (2H,d,J=8.8Hz), 11.91 (1H,s), 15.41 (1H,s).

c) 4-[1-Hydroxy-3-(2-hydroxy-4-trimethylsilylphenyl)-3-oxo-1-propenyl]benzoic Acid

To a solution of 370mg (1mmol) of methyl 4-[1-hydroxy-3-(2-hydroxy-5-trimethylsilylphenyl)-3-oxo-1-propenyl]benzoate in 60ml of ethanol was added 5ml of 2N sodium hydroxide solution at room temperature with stirring. The mixture was stirred at room temperature overnight, neutralized with 10% hydrochloric acid to pH 8, and evaporated H_2O was added to the residue and the mixture was acidified with 10%-hydrochloric acid to pH4. A deposited precipitation was collected by filtration, dried, and recrystalized from N,N-dimethylformamide and ethanol to give 175mg of yellow plates (yield 49%), m.p. 288-291 • C (decomp.).

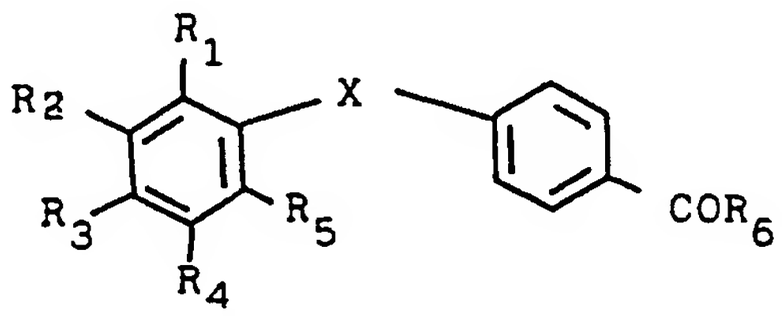
MS spectrum m/z: 356 (M^+).

^{1}H-NMR spectrum δ (DMSO-d_6)ppm: 0.27 (9H,s), 7.00-8.24 (8H,m).

It is to be understood that the invention is not to be limited to the exact details of operation, or to the exact compositions, methods, procedures, or embodiments shown and described, as modifications and equivalents will be apparent to one skilled in the art, and the invention is therefore to be limited only by the full scope of the appended claims.

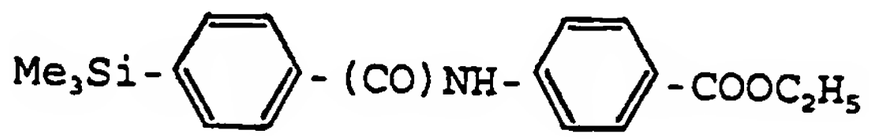
Claims

1. A benzoic acid derivative represented by the formula (I)



(I)

wherein R_1 represents hydrogen or lower-alkyl, R_2 and R_4 represent hydrogen, trimethylsilyl, or trimethylgermyl, R_3 represents hydrogen, lower-alkyl, trimethylsilyl, or trimethylgermyl, R_5 represents hydrogen, lower-alkyl, acetyl or hydroxy, at least one of R_2 and R_3 being trimethylsilyl or trimethylgermyl, and R_6 means hydroxy, lower-alkoxy, or a group of the formula $-NR_7R_8$, wherein R_7 and R_8 mean hydrogen or lower-alkyl, and X represents a group of the formula -CONH-, -NHCO-, -COO-, -OCO-, -COCH=CH-, -COCH=C(OH)-, or -CH=CH- except the compound



(p-Trimethylsilylbenzoyl-p-carbethoxy anilide)

2. A compound of claim 1 which is 4-[3,5-Bis(trimethylsilyl) phenylcarbamoyl]benzoic acid.

3. A compound of claim 1 which is 4-[3,5-Bis(trimethylsilyl) phenylcarboxamido]benzoic acid.

4. A compound of claim 1 which is 4-[3-[3,5-Bis(trimethylsilyl) phenyl]-3-oxo-1-propenyl]benzoic acid.

5. A compound of claim 1 which is 4-[3-[3,5-Bis(trimethylgermyl) phenyl]-3-oxo-1-propenyl]benzoic acid.

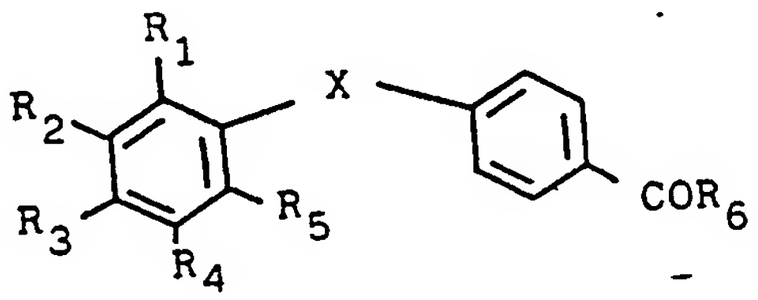
6. A compound of claim 1 which is 4-[1-Hydroxy-3-(2-hydroxy-5-trimethylsilylphenyl)-3-oxo-1-propenyl]-benzoic acid.

7. A differentiation-inducing agent for neoplastic cells, especially leukemia cells comprising as active differentiation inducing ingredient at least one compound as claimed in claim 1.

8. A therapeutic agent for psoriasis comprising as active ingredient at least one compound as claimed in claim 1.

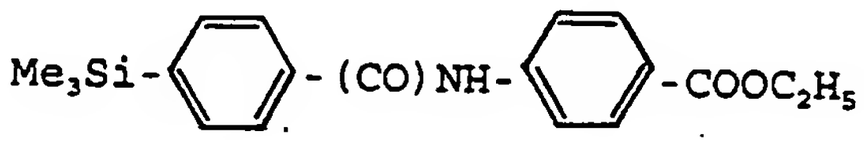
9. A therapeutic agent for immune and inflammatory diseases comprising as active ingredient at least one compound as claimed in claim 1.

10. A process for the preparation of a benzoic acid derivative represented by the formula (I):



(I)

wherein R_1, R_2, R_3, R_4, R_5, R_6 and X are as defined in claim 1, except the compound



(p-Trimethylsilylbenzoyl-p-carbethoxy anilide) comprising the steps of

(a) a compound represented by the formula (I), wherein X represents a group of the formula -CONH-, is prepared by acylation of a p-aminobenzoic acid or a derivative thereof with a functional derivative, such as the acid halide or ester, of a corresponding benzoic acid derivative, or

(b) a compound represented by the formula (I), wherein X represents a group of the formula -NHCO-, is prepared by acylation of a corresponding aniline derivative with a functional derivative, such as the acid halide or ester, of terephthalic acid, or

(c) a compound represented by the formula (I), wherein X represents a group of the formula -COO-, is prepared by acylation of a p-hydroxybenzoic acid or a derivative thereof with a functional derivative, such as the acid halide or ester, of a corresponding benzoic acid derivative, or

(d) a compound represented by the formula (I), wherein X represents a group of the formula -OCO-, is prepared by acylation of a corresponding phenol derivative with a functional derivative, such as the acid halide or ester, of terephtalic acid, or

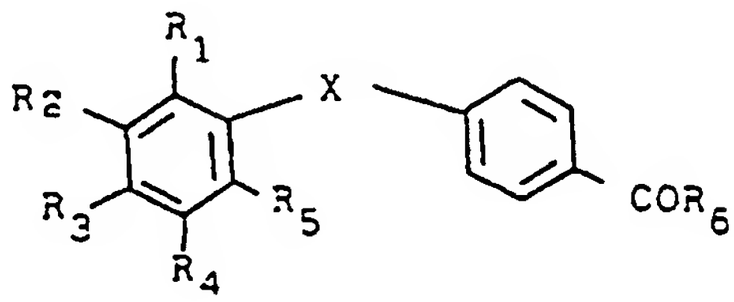
(e) a compound represented by the formula (I), wherein X represents a group of the formula -COCH=CH-, is prepared by condensation of a corresponding acetophenone derivative with a terephthalaldehydic acid or a derivative thereof in the presence of a base, or

(f) a compound represented by the formula(I), wherein X represents a group of the formula -COCH=C(OH)- and R_5 represents hydroxy, is prepared by rearrangement of an ester compound derived from a corresponding o-hydroxyacetophenone derivative and a terephthalic acid or a derivative thereof in the presence of an alkali catalyst, or

(g) a compound represented by the formula (I), wherein X represents a group of the formula -CH=CH-, is prepared by condensation of a corresponding benzylphosphonium salt with a terephthalaldehydic acid or a derivative thereof and the obtained compound is optionally hydrolyzed.

Patentansprüche

1. Benzoesäure-Derivat, dargestellt durch die Formel (I)



(I)

worin

R_1 Wasserstoff oder Niederalkyl darstellt,

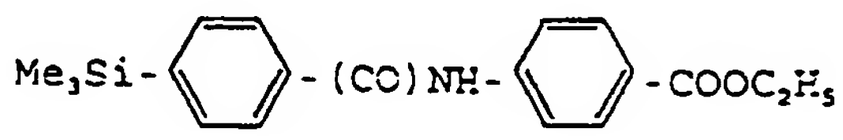
R_2 und R_4 Wasserstoff, Trimethylsilyl oder Trimethylgermyl darstellen,

R_3 Wasserstoff, Niederalkyl, Trimethylsilyl oder Trimethylgermyl darstellt,

R_5 Wasserstoff, Niederalkyl, Acetyl oder Hydroxy darstellt,

wobei wenigstens einer der Substituenten R_2 und R_3 Trimethylsilyl oder Trimethylgermyl ist, und

R_6 Hydroxy, Niederalkoxy oder eine Gruppe der Formel $-NR_7R_8$ bedeutet, worin R_7 und R_8 Wasserstoff oder Niederalkyl bedeuten, und X eine Gruppe der Formel -CONH-, -NHCO-, -COO-, -OCO-, -COCH=CH-, -COCH=C(OH)- oder -CH=CH- darstellt, mit Ausnahme der Verbindung



(p-Trimethylsilylbenzoyl-p-carbethoxyanilid).

2. Verbindung nach Anspruch 1, die 4-[3,5-Bistrimethylsilyl)phenylcarbamoyl]benzoesäure ist.

3. Verbindung nach Anspruch 1, die 4-[3,5-Bistrimethylsilyl)phenylcarboxamido]benzoesäure ist.

4. Verbindung nach Anspruch 1, die 4-{3-[3,5-Bistrimethylsilyl)phenyl]-3-oxo-1-propenyl}benzoesäure ist.

5. Verbindung nach Anspruch 1, die 4-{3-[3,5-Bistrimethylgermyl)phenyl]-3-oxo-1-propenyl}benzoesäure ist.

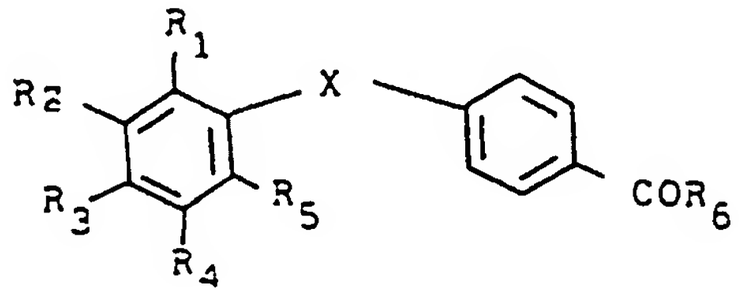
6. Verbindung nach Anspruch 1, die 4-[1-Hydroxy-3-(2-hydroxy-5-trimethylsilylphenyl)-3-oxo-1-propenyl]-benzoesäure ist.

7. Ein die Differenzierung induzierendes Mittel für neoplastische Zellen, insbesondere Leukämie-Zellen, umfassend als aktiven, die Differenzierung induzierenden Inhaltsstoff wenigstens eine Verbindung, wie sie in Anspruch 1 beansprucht ist.

8. Therapeutisches Mittel für Psoriasis, umfassend als aktiven Inhaltsstoff wenigstens eine Verbindung, wie sie in Anspruch 1 beansprucht ist.

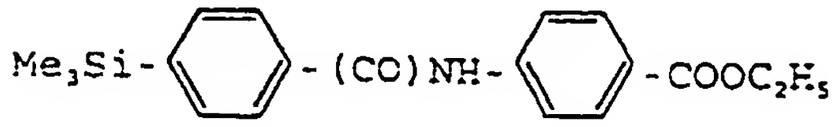
9. Therapeutisches Mittel für Immunerkrankungen und Entzündungs-Erkrankungen, umfassend als aktiven Inhaltsstoff wenigstens eine Verbindung, wie sie in Anspruch 1 beansprucht ist.

10. Verfahren zur Herstellung eines Benzoesäure-Derivats, das durch die Formel (I)



(I)

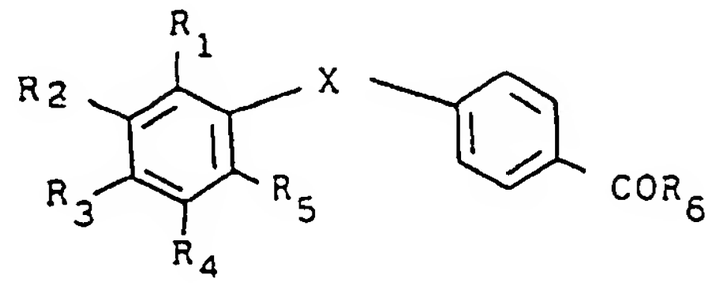
dargestellt wird, worin
R_1, R_2, R_3, R_4, R_5, R_6 und X die in Anspruch 1 angegebenen Bedeutungen haben, mit Ausnahme der Verbindung



(p-Trimethylsilylbenzoyl-p-carbethoxyanilid), umfassend die Schritte, in denen
(a) eine Verbindung der Formel (I), in der X eine Gruppe der Formel -CONH- darstellt, durch Acylierung einer p-Aminobenzoesäure oder eines Derivats derselben mit einem funktionellen Derivat, wie dem Säurehalogenid oder Ester eines entsprechenden Benzoesäure-Derivats hergestellt wird, oder
(b) eine Verbindung der Formel (I), in der X eine Gruppe der Formel -NHCO- darstellt, durch Acylierung eines entsprechenden Anilin-Derivats mit einem funktionellen Derivat, wie dem Säurehalogenid oder Ester der Terephthalsäure hergestellt wird, oder
(c) eine Verbindung der Formel (I), in der X eine Gruppe der Formel -COO- darstellt, durch Acylierung einer p-Hydroxybenzoesäure oder eines Derivats derselben mit einem funktionellen Derivat, wie dem Säurehalogenid oder Ester eines entsprechenden Benzoesäure-Derivats hergestellt wird, oder
(d) eine Verbindung der Formel (I), in der X eine Gruppe der Formel -OCO- darstellt, durch Acylierung eines entsprechenden Phenol-Derivats mit einem funktionellen Derivat, wie dem Säurehalogenid oder Ester der Terephthalsäure hergestellt wird, oder
(e) eine Verbindung der Formel (I), in der X eine Gruppe der Formel -COCH = CH- darstellt, durch Kondensation eines entsprechenden Acetophenon-Derivats mit einer Terephthalaldehydsäure oder einem Derivat derselben in Gegenwart einer Base hergestellt wird, oder
(f) eine Verbindung der Formel (I), in der X eine Gruppe der Formel -COCH = C(OH)- darstellt und R_5 Hydroxy darstellt, durch Umlagerung einer von einem entsprechenden o-Hydroxyacetophenon-Derivat und einer Terephthalsäure oder einem Derivat derselben abgeleiteten Ester-Verbindung in Gegenwart eines Alkali-Katalysators hergestellt wird, oder
(g) eine Verbindung der Formel (I), in der X eine Gruppe der Formel -CH = CH- darstellt, durch Kondensation eines entsprechenden Benzylhosphonium-Salzes mit einer Terephthalaldehydsäure oder einem Derivat derselben in Gegenwart einer Base hergestellt wird und die erhaltene Verbindung gegebenenfalls hydrolysiert wird.

Revendications

1. Un dérivé d'acide benzoïque représenté par la formule (I)



(I)

dans laquelle R_1 représente un hydrogéne ou un alkyle inférieur, R_2 et R_4 représentent un hydrogène, un triméthylsilyle ou un triméthylgermyle, R_3 représente un hydrogène, un alkyle inférieur, un triméthylsilyle ou un triméthylgermyle, R_5 représente un hydrogène, un alkyle inférieur, un acétyle ou un hydroxy, au moins l'un de R_2 et R_3 étant un triméthylsilyle ou un triméthylgermyle, et R_6 signifie un hydroxy, un alcoxy inférieur ou un groupe de formule $-NR_7R_8$ dans laquelle R_7 et R_8 signifient un hydrogène ou un alkyle inférieur et X représente un groupe de formule -CONH-, -NHCO-, -COO- -OCO- , -COCH = CH-, -COCH = C(OH)-, ou -CH = CH- à l'exception du composé

(p-triméthylsilylbenzoyl-p-carbéthoxy anilide).

2. Un composé de la revendication 1 qui est l'acide 4-[3,5-bis(triméthylsilyl)phénylcarbamoyl]benzoïque.

3. Un composé de la revendication 1 qui est l'acide 4-[3,5-bis(triméthylsilyl)phénylcarboxamido]-benzoïque.

4. Un composé de la revendication 1 qui est l'acide 4-[3-[3,5-bis(triméthylsilyl)phényl]-3-oxo-1-propényl]-benzoïque.

5. Un composé de la revendication 1 qui est l'acide 4-[3-[3,5-bis(triméthylgermyl)phényl]-3-oxo-1-propényl]benzoïque.

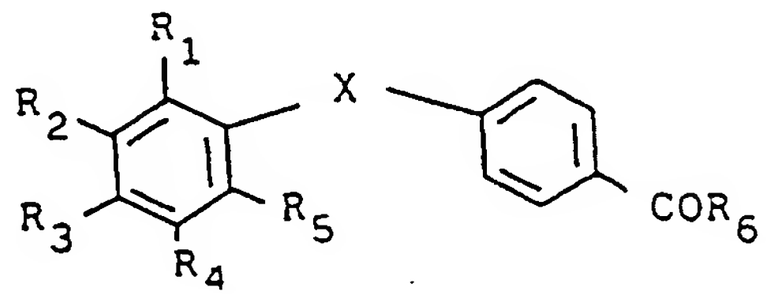
6. Un composé de la revendication 1 qui est l'acide 4-[1-hydroxy-3-(2-hydroxy-5-triméthylsilylphényl)-3-oxo-1-propényl]benzoïque.

7. Un agent induisant une différenciation des cellules néoplastiques, en particulier des cellules de la leucémie, comprenant comme principe actif induisant une différenciation au moins un composé tel que revendiqué dans la revendication 1.

8. Un agent thérapeutique pour le psoriasis comprenant comme principe actif au moins un composé tel que revendiqué dans la revendication 1.

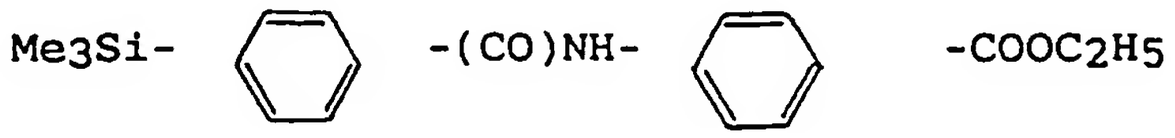
9. Un agent thérapeutique pour les maladies immunitaires et inflammatoires comprenant comme principe actif au moins un composé tel que revendiqué dans la revendication 1.

10. Un procédé pour la préparation d'un dérivé d'acide benzoïque représenté par la formule (I) :



(I)

dans laquelle R_1, R_2, R_3, R_4, R_5, R_6 et X sont tels que définis dans la revendication 1, à l'exception du composé



(p-triméthylsilylbenzoyl-p-carbethoxy anilide),

comprenant les étapes de

(a) un composé représenté par la formule (I), dans laquelle X représente un groupe de formule -CONH-, est préparé par acylation d'un acide p-aminobenzoïque ou d'un dérivé de celui-ci avec un dérivé fonctionnel, tel que l'halogénure ou l'ester de l'acide, d'un dérivé d'acide benzoïque correspondant ou acylation d'un dérivé aniline correspondant avec un dérivé fonctionnel tel que l'halogénure ou l'ester de l'acide, de l'acide téréphthalique ou

(c) un composé représenté par la formule (I), dans laquelle X représente un groupe de formule -COO-, est préparé par acylation d'un acide p-hydroxybenzoïque ou un dérivé de celui-ci avec un dérivé fonctionnel, tel que l'halogénure ou l'ester de l'acide, d'un dérivé d'acide benzoïque correspondant ou

(d) un composé représenté par la formule (I), dans laquelle X représente un groupe de formule -OCO-, est préparé par acylation d'un dérivé phénol correspondant avec un dérivé fonctionnel tel que l'halogénure ou l'ester de l'acide, de l'acide téréphtalique ou

(e) un composé représenté par la formule (I), dans laquelle X représente un groupe de formule -COCH = CH-, est préparé par condensation d'un dérivé acétophénone correspondant avec un acide téréphthaldéhydique ou un dérivé de celui-ci en présence d'une base ou

(f) un composé représenté par la formule (I), dans laquelle X représente un groupe de formule -COCH = C(OH)- et R_5 représente un hydroxy, est préparé par ré-arrangement d'un composé ester dérivé d'un dérivé o-hydroxyacétophénone correspondant et d'un acide téréphthalique ou d'un dérivé de celui-ci en présence d'un catalyseur alcalin ou

(g) un composé représenté par la formule (I), dans laquelle X représente un groupe de formule -CH = CH-, est préparé par condensation d'un sel de benzylphosphonium correspondant avec un acide téréphthalaldéhydique ou un dérivé de celui-ci et le composé obtenu est éventuellement hydrolysé.